Alzheimer’s disease: the status quo and the emergence of new hypotheses (and treatments)

Paola Sacchetti, Ph.D.
Assistant Professor
Director MS Neuroscience
Department of Biology
University of Hartford, CT
psacchett@hartford.edu
(860)768-5926
Today’s talk:

- Generalities about Alzheimer’s disease (AD)
- Pathology
- Beta amyloid hypothesis
- New hypotheses
- We, at UHart
AD is the most prominent form of dementia
Alois Alzheimer (1864-1915)

1906 He reported “A peculiar severe disease process of the cerebral cortex” which affected a woman in her fifties, Auguste D., and caused memory loss, disorientation, hallucinations and ultimately her death (at 55).

1907 His report noted distinctive plaques and neurofibrillary tangles in the brain histology.
Symptoms of disease progression

This is not normal aging

HHMI interactive AD project
Pathology of the disease - structural changes

- Smaller size
- Decreased Cortex (atrophy)
- Bigger ventricles
- Loss of Hippocampus & Entorhinal cortex
- Loss of Acetylcholine neurons

Davies P and Maloney, Lancet 1976
Bartus et al, Science 1982
Pathology of the disease - Microscopic changes

**Plaques** – Extracellular deposits
Mostly composed of
**Beta amyloid protein**
Glenner and Wong, *BBRC* 1984

**Tangles** of neurofilaments
Intracellular deposits
Mostly composed of
**Tau protein**
Brion JP et al, 1985
Wood et al, *PNAS* 1986
Distribution of toxic aggregates in AD brains
A SLOW MARCH

By the time that a person begins to experience the symptoms of Alzheimer’s disease, the condition is already well-established in the brain. The accumulation of amyloid-β, generally thought to be the first step in disease progression, could precede symptoms by 10–15 years. Tau accumulation occurs later, much closer to the onset of neurodegeneration.

10–15% of people with mild cognitive impairment* go on to develop dementia each year.

*Mild cognitive impairment is an abnormal decline in cognition that, unlike Alzheimer’s disease, does not affect daily living. It is considered to be a precursor to the condition.

8–10 YEARS
The average time for which a person with Alzheimer’s disease lives after diagnosis.
From genetics – Familiar AD – mutations were identified

APP - amyloid precursor protein gene on chromosome 21

The Beta amyloid Hypothesis

A DEEPER CUT
For the peptide amyloid-β to be released into the space between cells, the outermost portion of the membrane protein amyloid precursor protein (APP) must first be cleaved off by the enzyme β-secretase. Another enzyme, γ-secretase, then cuts the remaining membrane-bound portion of the protein, freeing amyloid-β. Because γ-secretase can cut APP at a number of sites, the length of amyloid-β can vary.
What do we know about AD?

1. Beta Amyloid is cleaved
2-3. Plaques form outside neurons and disrupt function
4. Neuroinflammation
5. Misfolded Tau aggregates inside neurons disrupting function
6. Misfolded Tau can spread between neurons

4 - Neuroinflammation
Structural & functional changes in non neuronal populations in response to toxic aggregates
Pro-inflammatory activity in the brain

Neuroinflammation seen through activation of supporting **astrocytes** and resident immune cells - **microglia**
Current medications

Types of drugs approved by the FDA – symptoms relief:
1. Cholinesterase inhibitors – “cholinergic hypothesis”: increase acetylcholine in the brain to help with memory formation
2. N-methyl-d-aspartate receptor antagonists: oppose effects of excitatory neurotransmitter glutamate

- No new AD drugs have been approved by the U.S. FDA since 2003
- Trials are focused on anti-Aβ and anti-tau agents
- Failures of over 400 trials of these drug classes raise questions as to whether Aβ and tau proteins are biomarkers or causes
New hypotheses or unfollowed hypotheses

We may finally know what causes Alzheimer’s – and how to stop it

Do Microbes Trigger Alzheimer’s?
The once fringe idea is gaining traction among the scientific community.

Herpes Viruses Implicated in Alzheimer’s Disease
The link between chronic gum disease and AD

Higher levels of an enzyme - gingipains, produced by the bacterium *Porphyromonas gingivalis*, have been found in the brains and CSF of AD patients.
The link between chronic gum disease and AD

The enzyme was found to cause mice to develop signs of AD
• dying neurons in Hippocampus
• higher levels of β-amyloid protein

The enzyme damaged tau and induced it to aggregate.

A drug anti-gingipain enzyme reduced β-amyloid production and neuronal death, and markers of inflammation.
Spirochetes & AD

6 genera, some causing Lyme disease (*Borrelia burgdorferi*), syphilis (*Treponema pallidum*), and gingivitis (several *Treponema*)

Polymicrobial biofilms formed over decades

Dementia observed in spirochetes-induced diseases; identified in many AD brains

Exposure induces chronic inflammatory response, Aβ plaques, cortical atrophy

J. Miklossy 2011
Herpes Virus Type I & AD

In 1,400 post-mortem AD brains, evidence of human herpes viruses 6A (HHV-6A) and 7 (HHV-7) in greater abundance in brain cortical regions.

Amyloid-β could prevent HSV1 infection and can bind and aggregate the HSV1 and HHV6 viruses.

Mice that had genetically elevated amyloid-β expression, once infected with HSV1—which can cause encephalitis—were protected against encephalitis, but also had increased amyloid deposits. W.A. Eimer et al. Neuron, July 12, 2018.

A recent drug trial targeting the virus (VALZ-PILOT) has been launched [TrialsGov - Valacyclovir 2017]
Pro-inflammatory activity in the brain as a response to pathogens’ attack

Amyloid plaques seen as an antimicrobial tool

J.U Adams The Scientist, 2017
“The Pathogen hypothesis”
Attention shifted to the microbiome

The brain microbiome contains hundreds of bacterial and fungal species

Comparing the brains of older and younger individuals with and without AD to identify viral residues.

Preliminary evidence shows that the brain microbiome is shifted and is linked to pro-inflammatory activity.

Drs. Tanzi & Moir, Harvard-Mass General
Gut-Brain-Axis and AD dysbiosis

Dysregulation observed in AD
Can Probiotics Supplementation Alter AD Pathology?

AD mice
- ADP n=5
- ADC n=5

Probiotic Supplementation 7mo-10mo
- Lactobacillus curvatus
- Lactobacillus plantarum

Immunohistochemistry Staining
- NeuN
- GFAP
- Iba1

Neurons
Astrocytes
Microglia
<table>
<thead>
<tr>
<th>Aim 1: Determine Effects of Probiotics on Neurons Death using NeuN+ Cell Counts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aim 2: Determine effects of Probiotics on supporting astrocytes using GFAP+ Cell Counts</td>
</tr>
<tr>
<td>Aim 3: Determine effects of Probiotics on microglia using IBA1+ Cell Counts</td>
</tr>
</tbody>
</table>

Can Probiotics Treatment Alter AD Pathology in a Transgenic Mouse Model?
Can Probiotics Treatment Alter AD Pathology in a Transgenic Mouse Model?

Aim 2: Determine effects of Probiotics on supporting astrocytes using GFAP+ Cell Counts

Aim 3: Determine effects of Probiotics on microglia using IBA1+ Cell Counts
Can Probiotics Treatment Alter AD Pathology in a Transgenic Mouse Model?

Aim 1: Determine Effects of Probiotics on Neurons Death using NeuN+ Cell Counts

Aim 3: Determine effects of Probiotics on microglia using IBA1+ Cell Counts
Can Probiotics Treatment Alter AD Pathology in a Transgenic Mouse Model?

Aim 1: Determine Effects of Probiotics on Neurons Death using NeuN+ Cell Counts

Aim 2: Determine effects of Probiotics on supporting astrocytes using GFAP+ Cell Counts
Possible therapeutics to combat neuronal loss

Possible therapeutics to combat neuroinflammation

Inexpensive, easy to administer therapeutics to combat costly, debilitating diseases

Can Probiotics Treatment Alter AD Pathology?
Acknowledgments

Probiotics

Melissa Stanley
MSN ’17; DG Scholar

Krista McMurry
MSN ’18

Destynie Medeiros
Honors BA’19; DG Scholar
Ribicoff recipient

Ketogenic Diet

Adam Silver, Ph.D.

Marwa Elamin
MSN ’17; DG Scholar

Nick Buitrago
MSN